IN THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Susanne MATHEUS et al. Examiner: KAUFMAN, CLAIRE M

Serial No.: 10/588,458 Group Art Unit: 1646

Filed: August 4, 2006 Confirmation No.: 5757

Title: **HIGHLY CONCENTRATED, LIQUID FORMULATIONS OF ANTI-EGFR ANTIBODIES**

REPLY BRIEF

Mail Stop **Appeal Brief- Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Reply Brief is submitted under 37 C.F.R. §41.41 in response to the Examiner's Answer mailed November 19, 2009.

1. Rejections withdrawn:

(None)

2. Rejections maintained:

The rejection of claims 1, 4, 8, 11, 16, 17 and 21-24 under 35 USC §103(a) has been sustained.

The rejection of claims 1-3, 5-10 and 12-17 under the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 1–13, 15-24 and 26–27 of US application no. 10/996,597 in view US patent no. 6,171,586 has been sustained. Although Appellants remarks in context to the obviousness rejection (filed with the Appeal Brief of August 19, 2009) addresses the basis for the rejection, the following arguments are provided to rebut the misplaced assertions made in the

Examiner's Answer.

Obviousness-type double patenting

Claims 1-3, 5-10 and 12-17 are rejected under the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 1–13, 15-24 and 26–27 of Mahler et al. (US application no. 10/996,597; *hereinfafter* "the '597 application") in view Lam et al. (US patent No. 6,171,586; *hereinafter* "the '586 patent"). This rejection is not supported on the record as a whole and should be reversed.

Lam (US patent No. 6,171,586; *hereinafter* "the '586 patent") discloses stable aqueous pharmaceutical formulations comprising an antibody, more specifically antibodies against CD18 and/or CD20. Lam further teaches that such antibodies are useful for the treatment of hemorrhagic shock and can be stored in a formulation having from about 0.1 mg/ml to about 50 mg/ml, preferably from about 0.5 mg/ml to about 25 mg/ml and most preferably from about 2 mg/ml to about 10 mg/ml of the antibody. See the entire section on BACKGROUND OF THE INVENTION section and the disclosure under "Preparation of the Formulation" section of the '586 patent. Lam does not teach or suggest antibody formulations comprising anti-EGFR antibodies, let alone the two specific anti-EGFR antibodies recited in the instant claims. Additionally, the preferred embodiments in Lam are directed to antibodies that are formulated at a *lower* concentration than the formulations claimed in the instant application. See, for example, the entire Examples section of the '586 patent. To this end, Example 1 of Lam discloses anti-CD18 antibodies and formulations thereof. As expressly taught by the disclosure in Table 5 of the '586 patent, Lam only discloses formulations at a concentration of ~1 mg/ml. Any skilled artisan can recognize that this formulation is significantly more dilute compared to the antibody formulations of the instant invention. In Example 2, Lam discloses anti-CD20 antibodies, which are initially prepared at low concentrations (about 2-3 mg/ml). Lam further teaches that such preparations can be concentrated to about 40 mg/ml, which confers stability for storage and pharmaceutical use. To do this, Lam starts with a bulk material of dilute antibody preparations, which are processed and further concentrated to a final concentration of 40 mg/ml. See the disclosure bridging columns 40–46 of the '586 patent. It is clear that even at its broadest interpretation, Lam only

discloses antibody preparations ≤ 50 mg/ml.

Mahler (US application No. 10/996,597; US publication No. 2005-0175611) discloses aqueous formulations of antibodies directed against EGFR which are suitable for parenteral administration, are well tolerated and are stable on storage at room temperature. Mahler generically discloses that Examples of such anti-EGFR antibodies are h425 and c225 antibodies. It is further taught that the anti-EGFR antibody in the formulation is at a concentration of from 0.1 mg/ml to 50 mg/ml, preferably from 2 mg/ml to 10 mg/ml, particularly preferably about 5 mg/ml. See, paragraphs [0019] to [0022] of the '611 publication. Mahler fails to teach or suggest the concentration ranges recited in Appellants' claims. More specifically, like the primary Lam reference, the preferred embodiments in Mahler are directed to antibodies that are formulated at a lower concentration than the formulations claimed herein. See the entire Examples section. As such, neither Lam nor Mahler provides any hint or suggestion that the recited anti-EGFR antibodies of the present invention (i.e., Mab c225 or Mab h425) can be prepared as highly concentrated formulations (50 mg/ml to 180 mg/ml). Nothing motivates a skilled worker to choose precisely Mab c225 or Mab h425 and combine it with precisely a generic process of concentrating proteins, especially since the details and examples of the cited references would point particularly to methods of concentrating other types of antibody molecules at much lower concentrations. Without such motivation, there can be no obviousness. *In re Baird*, 16 F.2d 380 (Fed.Cir. 1994).

The antibodies of Lam are not equivalent to the c225 or h425 monoclonal antibodies of the instant invention, insofar as they bind to different epitopes (CD18 and CD20, respectively) than the antibodies of the present invention. The anti-EGFR antibodies of the present application are prepared as stable, ready-to-use solutions having low viscosity, low application volumes for subcutaneous administration. Preparation of highly concentrated, liquid formulations of antibodies are afflicted with technical challenges and routine protocols for protein concentration are not always applicable for large protein biologics, such as, monoclonal antibodies, that are to be used in the clinical setting. For each individual antibody and especially for each monoclonal antibody, a specific method has to be developed to arrive at a preparation of highly concentrated formulations. For an antibody to remain biologically active, a formulation must preserve intact the conformational integrity of at least a core sequence of the protein's amino acids

while at the same time protecting the protein's multiple functional groups from degradation." Lam's disclosure in the BACKGROUND section of US patent No. 6,171,586 (cited in the Office Action) specifically addresses this issue. Lam recognizes that monoclonal antibodies poses a difficult problem with respect to high concentration, especially if pharmaceutically critical stabilizers should be omitted. As explicitly stated under MPEP §2145, "proceeding contrary to accepted wisdom in the art is evidence of non-obviousness. *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986)." Moreover, as explicitly stated under MPEP §2144.05, "A prima facie case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention [and that] Applicant can rebut a presumption of obviousness based on a claimed invention that falls within a prior art range by showing '(1) [t]hat the prior art taught away from the claimed invention...or (2) that there are new and unexpected results relative to the prior art.' *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 73 USPQ2d 1225 (Fed. Cir. 2004)." Such is clearly the case here. Lam teaches away from the subject matter of the instant claims. Accordingly, the antibody preparations, compositions, kits of the present invention, including methods for obtaining such are inventive over the cited references. Favorable reconsideration is respectfully requested.

For the above reasons and the reasons set forth in Appellants' Brief, it is submitted that the decision of the Examiner finally rejecting claims 1-3, 5-10 and 12-17, on appeal, is in error and should be reversed.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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